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从肠道菌群角度探讨非酒精性脂肪性肝病的研究进展

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摘　要

在过去的四十年中，非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)已成为最常见的慢性肝病，全球患病率约为成年人群的25%，其发病率持续上升，是全球的重大公共卫生问题。近年来，多项研究表明肠道菌群与NAFLD之间关系密切，NAFLD、慢性肝炎、肝硬化及肝癌等肝病患者均存在不同程度的肠道菌群失调，临床前研究证实了肠道菌群在NAFLD中的潜在因果作用。肠道菌群的组成、结构失衡会影响肠黏膜屏障及肠道代谢物，引起肠道通透性增加，产生肠源性内毒素血症，进而促进肝脏炎症反应，而肝损伤会进一步加重肠道通透性及全身炎症反应，由此形成恶性循环促进NAFLD的发生、发展。因而干预肠道菌群，可能是治疗及预防NAFLD的新策略。因此本文主要从肠道菌群的角度对NAFLD的发病机制及治疗作一综述。

关键词

肠道菌群，非酒精性脂肪性肝病，研究进展

Research Progress of Non-Alcoholic Fatty Liver Disease from the Perspective of Intestinal Flora

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Abstract

Over the past four decades, non-alcoholic fatty liver disease (NAFLD) has become the most common

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chronic liver disease, with a global prevalence of approximately 25% of the adult population, and its incidence continues to rise, making it a major public health NAFLD has become the most common chronic liver disease. In recent years, several studies have demonstrated the close relationship between intestinal flora and NAFLD. Patients with NAFLD, chronic hepatitis, cirrhosis and hepatocellular carcinoma, and other liver diseases have varying degrees of intestinal dysbiosis, and preclinical studies have confirmed the potential causal role of intestinal flora in NAFLD. Imbalance in the composition and structure of intestinal flora affects the intestinal mucosal barrier and intestinal metabolites, causing an increase in intestinal permeability, generating intestinal endotoxemia, which in turn promotes hepatic inflammatory response, and hepatic injury further exacerbates intestinal permeability and systemic inflammatory response, resulting in the formation of a vicious circle that promotes the onset and development of NAFLD. Thus, intervention of intestinal flora may be a new strategy for the treatment and prevention of NAFLD. Therefore, this article mainly reviews the pathogenesis and treatment of NAFLD from the perspective of intestinal flora.

Keywords

Intestinal Flora, Non-Alcoholic Fatty Liver Disease, Research Progress

1. 引言

非酒精性脂肪性肝病是遗传易感个体由于营养过剩、胰岛素抵抗引起的慢性进展性肝病，以肝细胞发生脂质沉积、脂肪变性为主要病理变化的一种慢性肝病，按其发病进程通常包括单纯性脂肪变性、非酒精性脂肪性肝炎(non-alco- holic steatohepatitis, NASH)，再到更晚期的疾病，包括晚期纤维化和肝硬化，最终可导致肝细胞癌、肝衰竭和死亡[1]-[4]，除肝脏相关并发症外，NAFLD 还增加了 2 型糖尿病(T2DM)、心血管和慢性肾脏疾病的风险[1]-[6]。既往有研究表明，过度氧化应激、炎症、肠屏障功能破坏、氧化和脂毒性脂质的蓄积、遗传因素以及固有免疫调节失衡可导致 NAFLD 的发生[7]-[12]。肠道菌群及其代谢物在疾病进展中有不可或缺的作用，肠道菌群失衡可以通过影响肠黏膜屏障完整性、炎症反应、菌群代谢物如短链脂肪酸(short chain fatty acids, SCFA)的生产、胆汁酸(Bile acids, Bas)代谢等多个途径参与肝脏脂质代谢及机体炎症免疫反应，最终促进 NAFLD 的发生发展[13]。肠道菌群及其代谢产物可通过门静脉进入肝脏，引起肝脏的炎症反应，影响肝脏的病理生理过程。本文将重点从肠道菌群的角度总结 NAFLD 的相关发病机制及治疗药物的研究进展，为靶向肠道菌群调节治疗 NAFLD 的药物研发提供参考。

2. 肠道菌群与 NAFLD

人体肠道微生物主要包括细菌、古生菌、病毒和真菌等数以万亿计的微生物，其中肠道细菌是目前肠道微生态研究的主要对象。健康个体的肠道细菌以拟杆菌门和厚壁菌门最为丰富。其他不太普遍的分类群包括变形菌、疣状微生物、放线菌、梭菌和蓝细菌[14]，肠道菌群通过参与宿主的能量代谢、炎症及免疫反应等多个方面影响人体健康[15] [16]。研究发现，肠道菌群失调在 NAFLD 疾病进展过程中起着关键的作用。肝脏主要通过门静脉连接到肠道，而肠－肝轴是肠道菌群和肝脏相互作用的主要机制[17]。一方面，肝脏中产生的生物活性物质，如胆汁酸和抗微生物分子，可以进入肠道调节肠道菌群的生长。另一方面，肠道微生物群的代谢产物可以随着门静脉循环进入肝脏，调节肝脏的功能。在 NAFLD 患者中，

肠道菌群失调可引起肠上皮屏障的破坏及代谢紊乱发生，促使致病菌及内毒素通过门静脉进入肝脏，促进 NAFLD 发病的炎症过程和脂肪堆积[18] [19]，此外，由于肝脏的功能失调，其分泌的生物活性物质发生改变，阻止了肠道生态系统的恢复，促进 NAFLD 进展的恶性循环。

肠道菌群的多样性在维持人类健康方面发挥着重要作用，而较低的 α-多样性通常与炎症、肥胖和胰岛素抵抗有关[20]。Stuart Astbury 等人发现，非酒精性脂肪性肝炎(NASH)患者的 α-多样性较低，肝硬化患者的 α-多样性进一步降低[21]。多项研究表明，NAFLD 中肠杆菌科、拟杆菌门和梭杆菌门增加，瘤胃球菌、粪杆菌属和粪球菌属的相对丰度均下降[22]-[24]。肠道菌群组成在 NAFLD 进展过程中也发生了变化，Nicolas Lanthier 等人的一项研究发现[25]：随着脂肪沉积和纤维化的开始，狭义梭菌的丰度显著降低。进一步的线性判别分析表明，大肠杆菌/志贺氏菌可能是纤维化的判别微生物。一项针对 110 例代谢相关性脂肪肝的研究证实[22]：大肠埃希菌与脂肪变性和坏死性炎症活性相关，而大肠埃希菌－志贺氏菌与纤维化和坏死性炎症活性相关。

3. 肠道菌群致病机制

3.1. 肠黏膜屏障损伤

肠黏膜屏障主要由机械、化学、微生物及免疫屏障组成，各屏障具有不同功能，相互作用，共同维持肠道稳态[26]。研究结果表明，肠屏障功能的改变，包括上皮、微生物、生物化学或免疫屏障相互作用调节的微小变化，可能导致代谢性疾病(包括 NAFLD)的发生[18] [27]。

正常情况下，保持稳定比例的肠道微生物可促进免疫系统的发育和成熟，并诱导局部产生抗菌肽和免疫球蛋白来维持维护肠道屏障的完整性[28]。肠道微生物群在食物发酵过程中产生的短链脂肪酸可激活肠结节样受体家族 3 结构域的炎症体，刺激 IL-18 的分泌[29]，调节肠上皮细胞对细菌产物的耐受性[30]，促进肠黏膜屏障的完整性。这类肠道微生物及其产物与肠道有益共生。

此外，已有研究证明 Bas 在维持肠黏膜屏障功能中有不可忽视的作用。Bas 作为信号分子主要与 FXR 和 TGR5 两种 Bas 受体相互作用和调节，在维持肠黏膜屏障的稳态中发挥重要作用[31]。肝脏产生的 Bas 可通过作用于肠道上皮细胞产生抗菌肽等抑菌物质起到直接或间接抑制致病菌生长的作用。此外，BAs 也可通过改变细菌群落结构直接而迅速地影响宿主代谢[32]。既往有研究表明，熊脱氧胆酸可以促进厚壁菌门与拟杆菌门的比例正常化并刺激富含胆盐水解酶(bilesalthydrolase, BSH)的细菌的生长来改善肠道微生物群的失衡[33]。在肝肠循环过程中，Bas 可激活核受体 FXR 诱导肠道保护基因表达，并通过破坏细菌细胞膜抑制细菌过度生长和黏膜损伤[34]。成纤维细胞生长因子 19 (fibroblast growth factor 19, FGF19)可由 FXR 调控其在肠道中的表达，FXR-FGF19 轴的激活通过恢复正常的 Bas 库来调节肠道微生物群[35]。肠道微生物群也可以通过生成多种消化酶来调节 Bas 的合成和运输，进一步影响 Bas 介导的消化、吸收、信号传导等功能，进而对肠道微生物屏障进行调节。例如肠道微生物群中的 BSH 可降低肠道 FXR 拮抗剂牛磺-β-鼠胆酸(tauro-β-muricholicacid, T-βMCA)的表达，从而调节 Bas 代谢[36]。

在 NAFLD 患者中，肝损伤可能引起肠黏膜缺血缺氧、肠动力障碍，有时可能伴随胆汁酸(Bas)排泄障碍，这些因素使得肠道细菌清除及排空减少，结肠菌群上移，最终导致共生菌群多样性降低，肠杆菌科、梭杆菌门等机会致病菌增加。饮食或环境变化(如高热量摄入或饮酒)也会导致肠道菌群的破坏(生态失调) [37]。例如，肥胖或 NAFLD 患者肠道细菌革兰氏阴性菌的数量显著增加，并表现出明显的内毒素血症[38]。此外，在肠道菌群失调时，SCFA 生成减少，肠道中 TNF-α、IL-1β 的含量显著上升，干扰肠黏膜紧密连接。肠道菌群失调产生的内源性乙醇影响黏蛋白糖基化，直接破坏肠黏液层[39]。中间产物乙醛破坏肠黏膜紧密连接[40]。肠道菌群失调导致肠黏膜生物屏障受损，加重肠道通透性及全身炎症反应，促进 NAFLD 进展。

3.2. 模式识别受体和病原体相关分子模式

模式识别受体(PRRs)识别病原体相关分子模式(PAMPs)及受损组织中的损伤相关分子模式(DAMPs)并随后激活先天性和适应性免疫的概念已在 1989 年描述[41]。PAMPs 通常是外源性的微生物产物，例如脂多糖(LPS)、肽聚糖(PGN)、细菌 DNA 和病毒双链 RNA (dsRNA)，是微生物生存的重要组成部分。DAMPs 主要来源于受损和/或垂死细胞释放的内源性产物，组织损伤碎片和能量代谢物[42]。肠道菌群失调损伤肠黏膜屏障，其可生成 PAMPs 通过肠－肝循环进入血液，促进肝脏损伤，而肝细胞受损生成的 DAMPs 也会进入循环，肝脏作为免疫器官，通过 PRRs 来识别循环和微环境中的 PAMPs 和 DAMPs 以对抗感染或损伤[43] [44]。有研究分别对 NAFLD 患者及高脂饮食诱导的 NASH 小鼠进行肝脏活检和血清检测，结果发现实验组的血清及肝组织的 LPS 和炎症因子(IL-1, IL-6, TNF-α)水平均高于正常对照组[45]。高脂饮食不仅会改变肠道菌群平衡，进一步损害肠道屏障完整性和肠道血管屏障，促进细菌产物如脂多糖(lipopolysaccharide, LPS)、乙醇及三甲胺等通过门静脉进入肝脏，加剧肝脏炎症和代谢异常[46]，还能促使脂质在肝脏中的积累，导致肝细胞损伤，产生 DAMPs 被 PRRs 识别，以激活炎性信号传导分子并介导肝脏炎症，促进 NFALD 的发展[43]。

目前已经发现的模式识别受体主要有 6 种[47] [48]：TLRs、C 型凝集素样受体(C-type lectin-like receptors, CLRs)、NLRs、维甲酸诱导基因样受体(retinoic acid inducible gene I-like receptors, RLRs)、AIM2 样受体(absent in melanoma 2-like receptors, ALRs)、环鸟苷酸－腺苷酸合成酶(cyclic GMP-AMP synthase, cGAS)。与肠道菌群所致炎症反应有关的 PRRs 主要是 TLRs 和 NLRs，本文着重介绍这两种 PRRs。

3.2.1. TLRs

越来越多的证据表明 TLRs 与 NAFLD 进展之间存在关联。迄今为止，已在哺乳动物中鉴定了 13 种功能性 TLRs，在人类中鉴定了 10 种已知的 TLRs (TLR1~TLR10) [49]。PAMPs (LPS、蛋白、聚糖和核酸等)可激活 TLRs 信号转导，刺激免疫细胞产生炎症因子和共刺激分子[50] [51]。TLRs 信号转导涉及髓系分化因子(MyD88)依赖性信号转导通路和 MyD88 非依赖性信号转导通路。在 Myd88 依赖性通路中，在与其相应配体结合后，除 TLR3 外，所有 TLRs 成员均通过 MyD88 转导信号，诱导级联反应，导致 NF-κB (nuclear factor kappa-B)活化，并导致多种促炎细胞因子的产生，包括肿瘤坏死因子-α (TNF-α)和白细胞介素 6 (IL-6) [52]。在 MyD88 非依赖性信号传导途径中，TLR3、TLR4 和 TLR5 使用含 Toll/IL-1R 结构域的衔接子诱导 IFN-β (TRIF)作为激活剂来介导下游信号，这也被称为 TRIF 依赖性途径[49] [53]。TRIF 对 TNF 受体相关因子 3 (TRAF3)的募集起重要作用。一旦被刺激，TRAF3 募集 IKK 相关激酶，TRAF 家族成员相关 NF-κB 结合激酶(TBK1)和 IKKI 的激活导致干扰素调节因子 3 (IRF3)激活、二聚化和易位至细胞核，进而激活干扰素(IFN)诱导的基因表达，并导致炎症介质的释放。TRIF 也可以通过其 TRAF6 结合基序直接结合 TRAF6。然后 TRAF6 以类似于 MyD88 依赖性途径的方式激活转化生长因子 β-活化激酶 1 (TAK1)，最终激活 NF-κB 和诱导炎性细胞因子。

有研究表明 TLR1、TLR2、TLR4、TLR5、TLR9 与 NAFLD 的发生发展密切相关[54] [55]。TLR1 分布广泛，识别与肠道菌群密切相关的细菌三酰化脂肽和脂蛋白[55] [56]。肠道细菌多样性减少、肠道菌群失调可促进 NAFLD 的进展，在 NAFLD 的发展过程中，TLR1 的表达与有害细菌 Holdemanella 属的丰度呈显著正相关，且与有益细菌的丰度呈显著负相关关系[56]。TLR2 通过 MyD88 依赖途径与 NOL1 和 NOL2 共同识别 PAMPs (肽聚糖(peptidoglycan，PGN)、脂磷壁酸(lipoteichoic acid, LTA)、脂阿拉伯甘露聚糖(lipoarabinomannan, LAM)、脂蛋白及脂肽等多种菌体成份)；有研究发现，微塑料(MP)破坏肠道菌群的稳态，激活肝脏中的 TLR2/NF-κB/NLRP3 通路，从而促进肝损伤[57]。TLR4 是最早发现的 TLRs 受体，其参与肝脂肪变性、肝纤维化和肝纤维化。LPS (脂多糖)是 TLR4 的经典配体，LPS 是革兰阴性细菌死亡

后细胞壁分解的产物，通过脂蛋白运载进入肠道毛细血管，最终汇入门静脉，肝脏是 LPS 的首个靶器官，LPS 通过 LPS 结合蛋白(LBP)-CD14 复合物诱导肝损伤，进而激活 TLR4，触发炎症级联反应[58]并增加肠道通透性[59]。TLR4 可与髓样分化蛋白 2 (MD2)相互作用，并识别 LPS 以激活 MyD88 依赖性 NF-κB 和 MAPK 通路，从而诱导促炎细胞因子产生[60] [61]。此外，TLR4 还可通过 MyD88 非依赖性信号传导途径，激活 TRAF3 和 TRAF6，引发Ⅰ型干扰素反应及刺激 NF-κB 引起炎症反应[51]。TLR5 识别革兰氏阴性菌中的鞭毛蛋白，在小鼠体内研究表明，鞭毛蛋白通过血管粘附蛋白 1 (VAP-1)起作用，诱导肝脏脂肪变性。VAP-1 是一种促炎蛋白，也参与内脏脂肪组织中细菌脂多糖诱导的炎症和脂解[62]。这反过来又促进了肝脏脂肪的积累[63]。最近的一项研究表明，大肠杆菌通过鞭毛蛋白介导的 TLR5/NF-κB 依赖性激活促进肝窦内皮细胞(LSEC)中 MASLD 的发生和内皮－间充质转化[64]。TLR9 存在于细胞内的囊泡中，很少存在于细胞膜上[65]。主要识别并结合细菌 DNA 中的未甲基化胞嘧啶－磷酸－鸟嘌呤(CpG 岛)，通过 MyD88 依赖途径触发信号级联，导致促炎性细胞因子应答[66]。TLR9 也可以被 NAFLD 患者血浆中高浓度肝细胞来源的线粒体 DNA (mtDNA)激活，mtDNA 可通过 TLR9 激活先天免疫系统，最终导致脂肪性肝炎、纤维化和胰岛素抵抗的发生[67] [68]。

3.2.2. NLRs

主要位于免疫细胞、上皮细胞、巨噬细胞和中性粒细胞的细胞质中，在免疫防御中起着重要作用。在人类中共确定了 23 个 NLR 成员[69]，NLR 分为四个亚组，包括 NLRA，NLRB，NLRC 和 NLRP (含 pyrin 结构域蛋白) [70]。NLRC 和 NLRP 是参与由病原体入侵期间细胞稳态破坏引起的炎症的关键受体。NOD1 和 NOD2 属于 NLRC 亚群，可识别所有革兰阴性细菌和部分革兰阳性细菌表面的 PGN 中的不同结构模体，引发炎症反应。NLRP6 在调节先天免疫和宿主防御中发挥关键作用[71] [72]，它可与 ASC 和 caspase-1 组装形成炎症小体，从而促进 IL-18 和 IL-1β 的成熟和分泌，并诱导细胞凋亡[73] [74]，致肠源性内毒素生成增多，形成内毒素血症，加重肝脏损伤。有研究也揭示了 NLRP6 基因缺失小鼠肠道植物群的改变与代谢性疾病之间的相关性，NLRP6 缺乏可通过 TLR4 和 TLR9 激动剂流入门静脉循环改变肠道菌群的组成[75]。微生物调节的代谢产物通过调节 NLRP6 炎性体信号传导来塑造肠道微环境[73]，NLRP6 可维持肠道环境的稳态和肠道植物群的组成，可有效防止 MASLD 发展为 MASH，甚至降低 MASLD 的发生率[76]。

3.3. 肠道菌群与代谢

3.3.1. SCFAs

短链脂肪酸(SCFAs)是肠道菌群发酵膳食纤维的主要代谢产物，其中乙酸(C2)、丙酸(C3)和丁酸(C4)是肠道中含量最高的 SCFAs。SCFAs 在机体代谢和免疫调节方面发挥着重要作用，如促进结肠蠕动、保护肠粘膜屏障、改变糖和脂代谢、参与免疫调节、改善电解质和营养素的吸收以及抗炎和抗肿瘤活性等[77]。其中，丁酸作为胃肠道微生物群的主要代谢底物，在肠屏障的功能中起着至关重要的作用[78]。丁酸抑制 ChREBP 和 SREBP-1 的活化，导致脂肪生成抑制[79]。动物体内研究表明，丁酸盐能通过激活过氧化物酶体增殖物激活受体 α (peroxisome proliferatorsactivated receptor α, PPARα)、抑制肝脏炎症和增强胰高糖素样肽 1 受体(glucagon-like peptide-1 receptor, GLP-1R)的表达来改善高脂饮食诱导的 NAFLD 和 NASH 进程[80] [81]。丙酸可减少超重和肥胖患者中的脂质积累[82]。血清代谢组学显示 NAFLD 患者血清中丁酸盐和丙酸盐水平降低[83] [84]，而加用富含产丙酸盐及丁酸盐的益生菌或膳食纤维，减少肝脏脂质积累和炎症反应，并改善肝脏胰岛素抵抗[30] [85] [86]。

3.3.2. 胆汁酸(Bas)代谢

肠道内的微生物群可以通过化学作用改变胆汁酸池的组成，进一步影响 NAFLD [87]。胆汁酸是胆固

醇在肝脏中合成，可分为初级和次级胆汁酸。法尼醇 X 受体(FXR)是核受体的超家族成员，其主要功能是调节胆汁酸代谢和肠肝循环。肠道菌群可激活 FXR 而间接影响胆汁酸的代谢[88]，FXR 可以下调肝脏 X 受体(LXR)和神经酰胺和固醇调节元件结合蛋白(SREBP-1c)的表达，以减少肝脏中脂肪酸和甘油三酯的合成，进一步减少脂肪生成和糖异生。FXR 还可激活成纤维细胞生长因子(FGF)15/19、PPARg、GLUT-4 和 GLP1 上调肝糖原合成，增加胰岛素的敏感性[89] [90]。既往有研究表明，肠道微生物可直接作用于 BAs，如产生胆汁盐水解酶(BSH)的细菌，BSH 可促使结合胆汁酸解偶联，导致偶联 BA 水平降低，而偶联 BA 可激活肠道 FXR 表达并促进肝脏脂肪变性[91]。

宿主胆汁酸反过来也能影响微生物的组成[92]。初级胆汁酸(PBAs)不仅通过直接抑制病原菌的过度生长来维持肠道菌群的稳态，还可作为肠道 FXR 的激动剂，激活其在回肠粘膜中的下游防御基因，保护肠上皮细胞免受细菌和微生物的破坏[93]。FXR 调控成纤维细胞生长因子 19 (FGF19)在肠道中的表达，FXR-FGF19 轴的激活可以恢复正常的 BAs 库来进一步调节肠道微生物群[35]。

3.3.3. 胆碱及其衍生物

胆碱及其衍生物，如 TMA 和 TMAO，是肠内微生物的主要代谢物[94]。含有甲胺、胆碱、磷脂酰胆碱和肉毒碱的食物将被变形菌和厚壁菌中三甲胺裂解酶的分解代谢分解成包括 TMA 的各种代谢物[95]。TMA 通过门静脉转移到肝脏，并被含黄素的单加氧酶转化为 TMAO，TMAO 可上调固醇调节元件结合蛋白 1c (sterol regulatory element binding protein-1c, SREBP-1c)的表达，SREBP-1c 可促进甘油三酯(triacyl-glycerol, TG)合成，加重肝脏脂肪变性[96]。与健康个体相比，NAFLD 患者的血清 TMA、TMAO 和胆碱水平显著升高[97]-[100]。有研究表明慢性暴露于高浓度的 TMAO 似乎与血管损伤和多种情况下纤维化倾向增强有关，包括代谢功能障碍相关脂肪性肝病、慢性肾病、心力衰竭等疾病[101]。此外 TMAO 可通过减少胆固醇转化为胆汁酸来影响脂质代谢和胆固醇稳态[102]，所以减少高胆碱食物摄入、抑制 TMA 的产生均能抑制或改善 NAFLD。

4. 治疗

4.1. 益生菌类制剂

近年来的研究显示肠道菌群失调与肝脏疾病密切相关[103]，因此通过益生菌、益生元、合生元类药物用以维持肠道内环境稳定是治疗 NAFLD 可行的研究方向[104]。益生菌是一种能通过调节宿主黏膜与系统免疫功能，保持肠道健康的活性微生物[105]。益生元作为益生菌的营养成分和底物，如乳果糖、低聚果糖和菊粉，可以促进如双歧杆菌和乳酸杆菌等有益肠道细菌的活性和选择性地生长，不仅使有害菌比例减少，还能促进机体抵抗病原微生物的入侵。合生菌是益生菌和益生元的结合体。作为安全的食用益生菌，乳酸杆菌和双歧杆菌不仅可以降低血液胆固醇水平[106]，还能改善肠炎症微环境，促进肠上皮细胞的生长和生存，并通过调节免疫系统和宿主防御来抑制病原菌[107]。一项 meta 分析表明，益生菌还可以通过 LPS/TLR4 信号通路下调血清 LPS 和肝脏 TLR4 从而延缓 NAFLD 的进展[108]。针对 NAFLD 患者，通过补充肠道内的益生菌、益生元可以减少肝损伤，并可能改善肝功能[109]。

4.2. 抗生素

抗生素有助于减少有害微生物过度增殖和细菌易位、减轻细菌肠道负担，延缓肝病进展[110]，一项研究表明，利福昔明有效缓解 MCD 饮食诱导的 NASH，逆转了菌群失调和肠道屏障功能障碍[111]。最近的一项研究表明，乳酸乳球菌素能够在减轻肠炎的同时将肠道和肝脏微生物组转变为与健康相称的新状态[112]。此外，索利霉素是一种高效抗生素，通过恢复肝功能和靶向肠道微生物组有益于 NAFLD 的

恢复[113] [114]；多粘菌素 B 和新霉素的组合减少了饮食诱导的 NAFLD 小鼠的脂质积累并改善了肠道屏障[115]。近年来，噬菌体疗法作为一种新的抗微生物剂受到了极大的关注。比如之前有研究表明，用噬菌体靶向根除 HiAlc-Kpn 有效地减轻了 NAFLD 模型小鼠中的细菌性自身免疫综合征和 NASH [116]。

4.3. 菌群移植

肠道菌群移植可能是抗 NAFLD 的一种新的治疗策略，有研究表明标准饮食小鼠的肠道菌群通过粪便微生物移植(FMT)至 NASH 小鼠肠道后，肠屏障功能较前改善，NASH 小鼠肠道菌群结构发生了明显改变，LPS 减少内毒素释放导致的炎症反应，肠道内有益菌群的丰度有所增加[117]。一项随机对照试验表明，FMT 可以通过改善肠道菌群失调来减少肝脏中的脂肪堆积，从而减轻脂肪肝疾病[118]。一项对 21 名的 NAFLD 患者进行纯素同种异体供体或自体 FMT 的研究中发现，与自体 FMT 相比，纯素同种异体供体 FMT 诱导了肠道微生物群谱的明显差异变化，包括锡拉真杆菌和潜在的益生菌韦氏白僵菌[119]，表明同种异体 FMT 更有益于对抗 NAFLD。因此，肠道菌群的移植可能成为预防和治疗 NAFLD 的新策略。

4.4. 其他

胰高血糖素样肽 1 (GLP-1)能够诱导胰岛素分泌，GLP-1 类似物或受体激动剂已被批准用于治疗 T2DM 和肥胖症。利拉鲁肽是一种 GLP-1 类似物，可降低 HFD 诱导的 NAFLD 小鼠的炎症和脂肪堆积，并使血糖参数和肠道微生物群组成正常化[120]。有研究证明，每日摄入维生素 C 后，NAFLD 患者的肝功能、胰岛素敏感性和肠道微生物群多样性增加[121]。小檗碱(BBR, $C_{20}H_{18}NO_4$)是一种主要从植物中提取的含氮天然碱性有机化合物，BBR 的功能包括降脂、调节代谢紊乱和增强胰岛素敏感性[122]，有研究证明，BBR 直接影响肠道微生物群来调节脂质代谢[123]-[126]。槲皮素是一种多酚类黄酮，具有抗细胞凋亡、抗氧化、抗炎和抗癌活性，其通过 toll 样受体 4/NF-κB 信号通路恢复脂质代谢和肠道菌群平衡[127]。四妙方由黄柏、苍术、薏苡仁、牛膝按照质量比 2:1:2:1 组成，具有清热利湿功效其显著改变了肠道菌群的组成和丰度，尤其是增加 *Akkermansia muciniphila* 的丰度特别明显[128]。

5. 总结与展望

随着人类生活方式的改变，NAFLD 发病率呈上升趋势，已成了发达国家慢性肝脏疾病的最常见的病因。但目前对于 NAFLD 的发病机制尚未完全了解，目前尚无正式获批的治疗药物。肠道菌群是近年来的研究热点，其与 NAFLD 的发病、进展及治疗有密不可分的联系。肠道菌群及其代谢产物可以通过改变肠道的免疫状态，进一步增加肠道通透性，引起肝脏的炎症反应，肠道微生物群有望成为 NAFLD 的新型生物标志物和治疗靶点。重建肠道微生态平衡可以延缓 NAFLD 病变进展，益生菌类制剂、抗生素治疗和粪便移植，已成为预防和治疗 NAFLD 的新策略。一些批准用于治疗糖尿病的药物及一些具有抗氧化、抗炎作用的维生素被创新性地用于研究治疗 NAFLD；中西医结合对于防治 NAFLD 亦具有巨大优势与广阔前景。而 NAFLD 发病机制复杂，未来有必要结合肠道基因组学、代谢组学和蛋白质组学等对肠道微生物、菌群代谢产物和影响疾病的分子机制之间的关系进行深入研究，而 16S rRNA 测序、代谢组学和宏基因组学等技术的快速发展使得能够在与 NAFLD 相关的众多临床研究中识别微生物组特征、肠道微生物源性代谢物谱的改变以及微生物基因及组成，对建立以肠道菌群或其代谢物为靶点的 NAFLD 治疗策略具有重要意义，为治疗 NAFLD 提供更多的新方法、新思路。

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